Derivation of primordial germ cells from human embryonic and induced pluripotent stem cells is significantly improved by coculture with human fetal gonadal cells.

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Public Summary:

Scientific Abstract:
The derivation of germ cells from human embryonic stem cells (hESCs) or human induced pluripotent stem (hIPS) cells represents a desirable experimental model and potential strategy for treating infertility. In the current study, we developed a triple biomarker assay for identifying and isolating human primordial germ cells (PGCs) by first evaluating human PGC formation during the first trimester in vivo. Next, we applied this technology to characterizing in vitro derived PGCs (iPGCs) from pluripotent cells. Our results show that codifferentiation of hESCs on human fetal gonadal stromal cells significantly improves the efficiency of generating iPGCs. Furthermore, the efficiency was comparable between various pluripotent cell lines regardless of origin from the inner cell mass of human blastocysts (hESCs), or reprogramming of human skin fibroblasts (hIPS). To better characterize the iPGCs, we performed Real-time polymerase chain reaction, microarray, and bisulfite sequencing. Our results show that iPGCs at day 7 of differentiation are transcriptionally distinct from the somatic cells, expressing genes associated with pluripotency and germ cell development while repressing genes associated with somatic differentiation (specifically multiple HOX genes). Using bisulfite sequencing, we show that iPGCs initiate imprint erasure from differentially methylated imprinted regions by day 7 of differentiation. However, iPGCs derived from hIPS cells do not initiate imprint erasure as efficiently. In conclusion, our results indicate that triple positive iPGCs derived from pluripotent cells differentiated on hFGS cells correspond to committed first trimester germ cells (before 9 weeks) that have initiated the process of imprint erasure.